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10α-Hydroxy-1-oxoeremophila-7(11),8(9)-dien-12,8-olide

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Key indicators

Single-crystal X-ray study
T = 289 K
Mean σ(C–C) = 0.004 Å
R factor = 0.039
wR factor = 0.084
Data-to-parameter ratio = 10.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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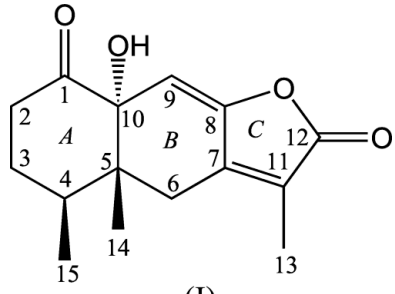
In the title compound, $C_{15}H_{18}O_4$, the methyl groups adopt a *syn* conformation, with the hydroxy group in an *anti* conformation relative to both methyl groups. The molecules are linked by intermolecular O—H···O hydrogen bonds involving a carbonyl and a hydroxyl group.

Comment

Sesquiterpenoids have received much attention on account of their structurally novel carbon skeletons and bioactivity (Fraga, 1995, 1996, 1997, 1998, 1999*a*,*b*, 2000; Peng *et al.*, 1997; Shi *et al.*, 1999; Wu *et al.*, 2004*a*,*b*; Yang *et al.*, 2002). An eremophilane-type sesquiterpenoid, 10α-hydroxy-1-oxoeremophila-7(11),8(9)-dien-12, 8-olide, (I), was isolated from the medicinal plant *Ligularia virgaurea* spp. oligocephala Good, which is used for the treatment of stomach ache and nausea (Wu 1985). The structure of (I), obtained by spectroscopic methods, was previously reported (Wu *et al.*, 2004*b*). The hydroxyl group on C-10 was established as being α-oriented by the larger coupling constant between H-3β (axial bond) and H-4α (axial bond), $J_{3\beta,4\alpha}$ = 13.6 Hz, in accordance with 4β,5β-Me (Massiot *et al.*, 1990). The crystal structure analysis of (I) was undertaken to establish the structure and relative stereochemistry unambiguously.



(I)

Cytotoxicity against selected cancer cells human promyelocytic leukemia (HL-60), human ovarian (HO-8910) and human lung epithehial (A-549) of compound (I) were measured *in vitro* using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method (Niu *et al.*, 2002; Toume *et al.*, 2004). Compared to etoposide (VP-16), compound (I) exhibited no significant inhibitory effects with IC_{50} values over 100 μ*M*.

An *ORTEP3* drawing (Farrugia, 1997) of the molecule is shown in Fig. 1. The bond lengths and angles have normal values (Allen *et al.*, 1987), with the following average values (Å): Csp^3—Csp^3 = 1.535 (3), Csp^3—Csp^2 = 1.508 (3), Csp^2—Csp^2 = 1.393 (3), C═O = 1.205 (3) and C—O = 1.411 (3). Ring

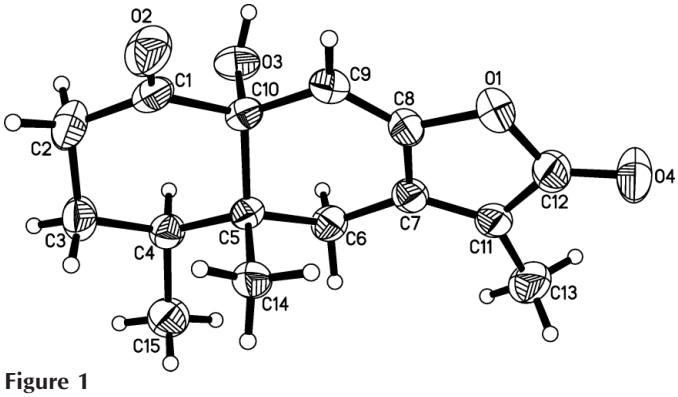


Figure 1
ORTEP3 (Farrugia, 1997) plot of the title compound. Displacement ellipsoids are drawn at the 50% probability level.

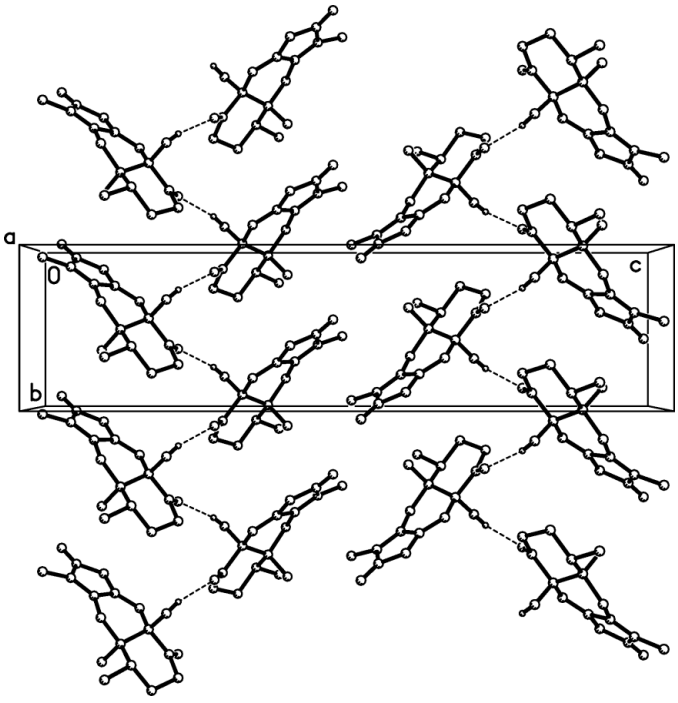


Figure 2
The molecular packing of (I), viewed along the *a* axis. Dashed lines represent O—H···O hydrogen bonds. Only the H atoms involved in hydrogen bonding are shown..

A is in a flattened chair conformation, with average torsion angles of 52.6 (3)°. Ring *C* is almost planar with a mean torsion angle of 0.98 (2)°. The torsion angle C6—C7—C8—C9 is 0.0 (4)° and C7—C8—C9—C10 is 2.6 (4)°; atoms C6–C10 are almost coplanar with ring *C*, and ring *B* adopts an envelope conformation.

The X-ray analysis of (I) shows that the hydroxyl group with α-orientation is located on C10 and the methyl-14 and the methyl-15 groups with β-orientation are located on C5 and C4, as reported previously based on spectroscopic methods (Wu *et al.*, 2004*b*). An interesting feature of the packing of the structure is that two methyl groups, C4—C15 and C5—C14, exhibit a *syn* conformation, and the hydroxyl group, C10—O3, exhibits an *anti* conformation with respect to the two methyl groups, even though *MM2* calculations indicate that this conformer should be around 3.9 kcal mol^{-1} less stable than C4—C15 and C10—O3 exhibiting a *syn* conformation and C5—C14 exhibiting an *anti* conformation. It is suggested that the compound crystallizes in this conformation in order to facilitate the formation of classical hydrogen bonds. The crystal packing is stabilized by intermolecular O—H···O hydrogen bonds involving the hydroxyl group and the C1-carbonyl group (Table 1). The hydrogen bonds link the molecules into chains along the *b* axis (Fig. 2).

Experimental

The dried and powdered roots of *Ligularia virgaurea* spp. oligocephala Good (4.0 kg) were extracted three times with 95% EtOH at room temperature. After evaporation under reduced pressure, the residue was then suspended in water and extracted successively with petroleum ether (333–363 K), EtOAc and *n*-BuOH. The EtOAc extract (75 g) was separated by repeated silica gel (200–300 mesh) column chromatography and recrystallization, giving compound (I) (yield 7 mg; m.p. 450–451 K; optical rotation: $[\alpha]_D^{25}$ −87.0°). Crystals suitable for X-ray diffraction measurements were obtained by slow evaporation of a solution of (I) in $CHCl_3/CH_3OH$ at room temperature. The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method was reported in the literature (Niu *et al.*, 2002; Toume *et al.*, 2004).

Crystal data

$C_{15}H_{18}O_4$
M_r = 262.29
Orthorhombic, $P2_12_12_1$
a = 6.885 (2) Å
b = 6.969 (2) Å
c = 27.348 (9) Å
V = 1312.2 (7) Å^3
Z = 4
D_x = 1.328 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 38 reflections
θ = 4.8–14.6°
μ = 0.10 mm^{-1}
T = 289 (2) K
Block, colourless
0.62 × 0.24 × 0.10 mm

Data collection

Siemens P4 diffractometer
ω scans
Absorption correction: none
1943 measured reflections
1810 independent reflections
1255 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 27.8°
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 9$
$l = -1 \rightarrow 35$
3 standard reflections
every 97 reflections
intensity decay: 2.8%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.084
S = 0.91
1810 reflections
180 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0416P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.013 (2)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3*O*···O2^{i}	0.82	2.10	2.906 (2)	169

Symmetry code: (i) $-x, y-\frac{1}{2}, -z+\frac{1}{2}$.

All H atoms were placed in calculated positions (O—H = 0.82 Å and C—H = 0.93–0.98 Å) and allowed to ride on the carrier atom, with U_{iso}(H) values constrained to be $1.5U_{eq}$ of the carrier atom for

methyl H atoms and $1.2U_{eq}$ for the remaining H atoms. Friedel reflections were merged before the final refinement because of the absence of significant anomalous scattering effects.

Data collection: *XSCANS* (Siemens 1994); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Bruker 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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